Conferences and Reviews

Applying the Results of Large Clinical Trials in the Management of Acute Myocardial Infarction

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Mortality from acute myocardial infarction has declined in recent years, largely due to the widespread application of new pharmacologic and mechanical interventions that have been tested in large, prospective, randomized clinical trials. For practicing generalists, we review the key data from such trials that have shaped the current management of patients with acute myocardial infarction. We discuss the roles of thrombolytic therapy, coronary angioplasty, nitrates, β- and calcium channel blockers, angiotensin-converting-enzyme inhibitors, magnesium, and antiarrhythmic and antithrombotic agents. In addition, we highlight critical unanswered questions in the management of this disorder.

(Sweeney JP, Schwartz GG: Applying the results of large clinical trials in the management of acute myocardial infarction. West J Med 1996; 164:238-248)

Coronary heart disease accounts for 700,000 deaths per year in the United States, with acute myocardial infarction (MI) accounting for about a third of these fatal events.[1,2] This article is intended for practicing physicians. We distill the results of the large, randomized clinical trials that have shaped the current optimal management of patients with acute MI, focusing on interventions that ordinarily would be implemented during the initial hospital admission for this disorder. The randomized trials discussed here have demonstrated that pharmacologic and mechanical interventions can reduce the morbidity and mortality from myocardial infarction if employed in appropriate patients.

Treating physicians, however, must never lose sight of three basic therapeutic goals in coronary care: relieving symptoms of ischemic pain or heart failure; assessing and optimizing hemodynamics; and assessing and treating serious rhythm disturbances. To review these fundamental principles of coronary care, readers are directed to a contemporary textbook of cardiology or internal medicine. The pursuit of these basic therapeutic goals may sometimes take precedence over the application of the results of the large clinical trials that are the focus of this review. Therapy must always be tailored to the individual patient, and it must be recognized that the general recommendations that follow may not apply to all patients with acute MI.

Thrombolytic Therapy

Acute MI results from prolonged ischemia, leading to myocardial necrosis. In most cases, this event is due to acute coronary artery thrombosis. Rare causes, including coronary artery spasm, systemic hypercoaguable states, and coronary artery dissection, are well recognized; these causes will not be the focus of the following discussion, however.

The primary event in the vast majority of acute MIs appears to be rupture of a lipid-rich coronary artery plaque. Once rupture occurs, underlying collagen and other subintimal substances are exposed, leading to platelet adhesion and aggregation and activation of the coagulation cascade. These events lead to acute coronary artery thrombosis and ischemia in the distribution of the affected vessel.[1,3,4] A classic angiographic study of Q-wave MI in 1980 identified thrombotic occlusion of an epicardial coronary artery as the proximate cause of acute MI in most infarctions.[5] This led to the development of both pharmacologic and mechanical strategies to reverse this thrombotic process, restore coronary perfusion, and possibly save myocardium at risk. Most of the effort has focused on the administration of thrombolytic drugs. The currently available agents include recombinant tissue plasminogen activator (t-PA), streptokinase, anistreplase (anisoylated plasminogen-streptokinase activator complex), and urokinase.

Placebo-controlled studies in the mid-1980s clearly showed that intravenous (IV) thrombolytic therapy results in improved survival. Although some of the benefit of coronary thrombolysis is likely due to the salvage of jeopardized myocardium, resulting in better left ventricular function, the substantial improvement in survival with thrombolytic therapy is disproportionate to the

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
CABG = coronary artery bypass grafting
GISSI = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico
GISSI-2, -3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [trial]
INR = international normalized ratio
ISIS-2, -3, -4 = Second, Third, and Fourth International Study of Infarct Survival
IV = intravenous
LIMIT-2 = Second Leicester Intravenous Magnesium Intervention Trial
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
RESCUE = Randomized Evaluation of Salvage Angioplasty With Combined Utilization of Endpoints
SWIFT = Should We Intervene Following Thrombolysis? [trial]
TIMI II, IIIB = Thrombolysis in Myocardial Infarction [trials] phase II, IIIB
t-PA = tissue plasminogen activator

modest improvement in left ventricular function. It appears that benefit may be derived from a patent infarct-related coronary artery, independent of myocardial salvage.[6] Overall, the use of IV thrombolytic agents within about six hours of the onset of symptoms of acute MI results in a 25% to 30% reduction in mortality, from about 10% to about 7% (Figure 1).[1,7]

Which Patients Should Receive Thrombolytic Agents?

The generally accepted indications and contraindications for thrombolytic therapy are shown in Tables 1 and 2, respectively. Patients presenting with ST-segment elevation in the anterior leads within six hours of the onset of pain clearly benefit from thrombolytic therapy, with reductions of both in-hospital and late mortality. A trend toward a reduction in mortality has been noted in patients with inferior-wall MI (ST-segment elevation in leads II, III, and aVF); a statistically significant reduction in mortality has not been demonstrated, however.[7] Nonetheless, it is reasonable to administer a thrombolytic agent in patients with inferior-wall infarction, especially in cases

TABLE 1.—Characteristics of Candidates for Thrombolysis

Characteristic	Candidates: Optimal*	Candidates: Acceptable†
Symptom duration, hr	<6	Between 6 and 24
Location of MI by ECG.....	Anterior wall	Nonanterior wall
Contraindications‡	No absolute or relative contraindications	Relative contraindication(s) only

ECG = electrocardiogram, MI = myocardial infarction

*An optimal candidate would possess all of the characteristics listed in the left column.
†An acceptable candidate may possess one or more characteristics listed in the right column.
‡See Table 2.

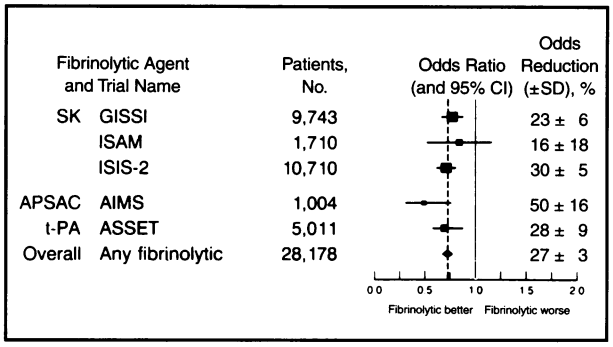

Figure 1.—Mortality reduction is shown in large, placebo-controlled trials of intravenous thrombolytic therapy for acute myocardial infarction. Overall (pooled) data indicate a 27% ± 3% reduction in mortality with thrombolytic therapy (from Reeder and Gersh[1]). AIMS = APSAC Intervention Mortality Study, APSAC = anistreplase (anisoylated plasminogen-streptokinase activator complex), ASSET = Anglo-Scandinavian Study of Early Thrombolysis, CI = confidence interval, GISSI = Gruppo Italiano per lo Studio della Strepochinasi nell'Infarto Miocardico, ISAM = Intravenous Streptokinase in Acute Myocardial infarction, ISIS-2 = 2nd International Study of Infarct Survival, SD = standard deviation, SK = streptokinase, t-PA = tissue plasminogen activator

suggesting a more complex infarction—that is, those with hemodynamic compromise, right ventricular involvement, or widespread electrocardiographic changes—with a low to moderate risk of bleeding. Patients presenting with new left bundle branch block and a clinical history consistent with acute MI also appear to benefit from thrombolytic therapy.[7] Several studies have investigated whether patients presenting with new ischemic ST-segment depression—that is, clinical syndromes of unstable angina or non–Q-wave MI—benefit from thrombolytic therapy. Despite the fact that many of these patients have angiographic evidence of coronary thrombi, neither the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI), the Second International Study of Infarct Survival (ISIS-2), nor the Thrombolysis in Myocardial Infarction phase IIIB (TIMI IIIB) trial demonstrated a survival benefit from thrombolytic therapy in such patients.[8-10]

Elderly patients are at a higher risk for bleeding, particularly intracranial bleeding, as a complication of thrombolytic therapy. This has led to reluctance on the part of some clinicians to administer these agents to these patients. Data from the Fibrinolytic Therapy Trialists' Collaborative Group, which pooled results from several major trials, demonstrated that there are larger proportional reductions in mortality among younger patients than among elderly patients.[7] The absolute reduction in mortality with thrombolytic therapy may actually be greater in elderly patients, however: Data from the ISIS-2 study revealed that combined streptokinase and aspirin use markedly reduced mortality from 23.8% to 15.8% in patients older than 70 years, compared with a reduction in mortality from 10.6% to 6.1% in patients younger than 70 years (Figure 2).[9,11] Therefore, no arbitrary upper age limit should be

TABLE 2.—Contraindications to Thrombolytic Therapy

Contraindication	Example
Absolute	Active bleeding
	Known intracranial tumor
	Stroke within 6 mo
	Major surgical procedure, gastrointestinal hemorrhage, or major trauma within 6 wk
	Head trauma within 1 mo
	Any clinical evidence of acute aortic dissection
	Bleeding diathesis or chronic liver disease with portal hypertension
Relative	History of recent gastrointestinal bleeding or active peptic ulcer
	Cardiogenic shock—consider emergent PTCA instead
	Uncontrolled hypertension—≥165/95 mm of mercury
	Prolonged or traumatic cardiopulmonary resuscitation
	Remote history of cerebrovascular disease
	Proliferative diabetic retinopathy

PTCA = percutaneous transluminal coronary angioplasty

imposed for thrombolytic therapy for acute MI. Rather, thrombolytic therapy should be considered for any patient, regardless of age, after a careful evaluation for indications and contraindications.

Hypertension increases the risk of intracranial hemorrhage as a complication of thrombolytic therapy. Hypertension at the time of thrombolytic drug administration—defined in one study as a systolic blood pressure ≥165 mm of mercury, diastolic blood pressure ≥95 mm of mercury, or both[12]—is a stronger risk factor for cerebral hemorrhage than a previous history of hypertension. Every attempt should be made to reduce the blood pressure below these limits before administering a thrombolytic drug. Patients with a history of hypertension are also at increased risk for aortic dissection, with signs and symptoms that may mimic those of acute MI. Clinical evidence suggesting aortic dissection is an absolute contraindication to thrombolytic therapy.

Timing of Thrombolytic Therapy

Perhaps the most important consideration in the use of a thrombolytic agent is that the time from the onset of symptoms to the administration of the drug bears a strong, inverse relationship to the ensuing reduction in mortality. Efficacy is clearly and sharply decremental over the first few hours after symptoms start. The improved survival from treatment with thrombolytic agents is related in part to myocardial salvage—that is, a reduction in the ratio of ultimately infarcted to initially jeopardized myocardium. The time dependence of myocardial salvage has been demonstrated in studies of dogs that showed that infarction is essentially complete within four to six hours of coronary artery occlusion.[6] Data from the ISIS-2 trial, however, revealed a survival benefit from aspirin and streptokinase use that persisted through 24 hours after the onset of symptoms.[9] In addition, results from the Late Assessment of Thrombolytic Efficacy (LATE) trial revealed a survival benefit from t-PA use in patients treated 6 to 12 hours from the onset of pain.[13] The mechanisms for the benefit of late reperfusion may include the prevention of necrosis in infarct border zones, improved electrical stability of reperfused myocardium, and attenuation of postinfarction ventricular enlargement.[6] Thus, it appears that administering a thrombolytic agent 6 to 12 hours (and perhaps as long as 24 hours) from the start of pain confers a survival benefit, albeit reduced from earlier reperfusion. It must be reemphasized that because the benefit of thrombolytic therapy is decremental with the passage of time, it is imperative that treating physicians pursue an early and accurate diagnosis of acute MI to achieve the maximal benefit of thrombolytic therapy. In fact, a recent European report indicates that prehospital thrombolytic therapy, administered by emergency medical personnel, reduces cardiac mortality compared with treatment after arrival at a hospital (median treatment time, 55 minutes later).[14]

Which Thrombolytic Agent Should Be Administered?

Three trials—ISIS-3,[15] GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico),[16]

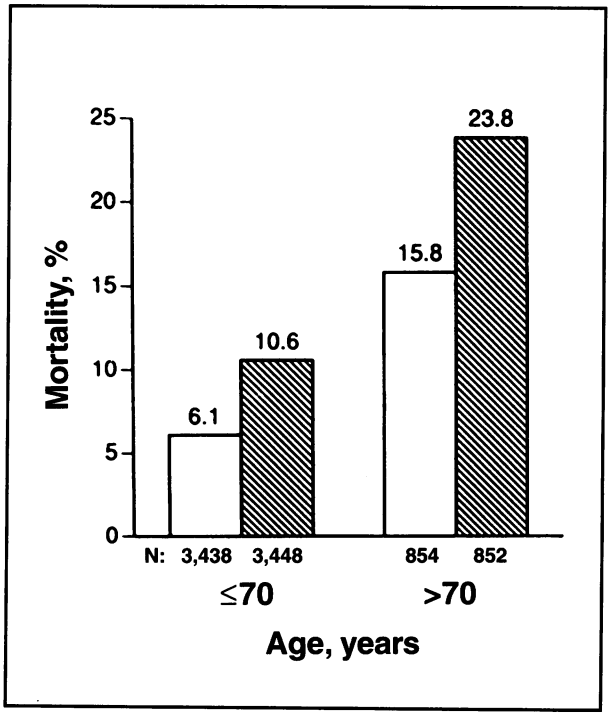

Figure 2.—The graph shows the mortality from acute myocardial infarction in the 2nd International Study of Infarct Survival, dichotomized by age 70 or younger or older than 70 years. The white bars represent patients who received streptokinase and aspirin, and the shaded bars represent the group receiving placebo. Although older patients have higher mortality, with or without thrombolytic therapy, they achieve a greater absolute reduction in mortality with thrombolytic therapy (from Muller and Topol[11]).

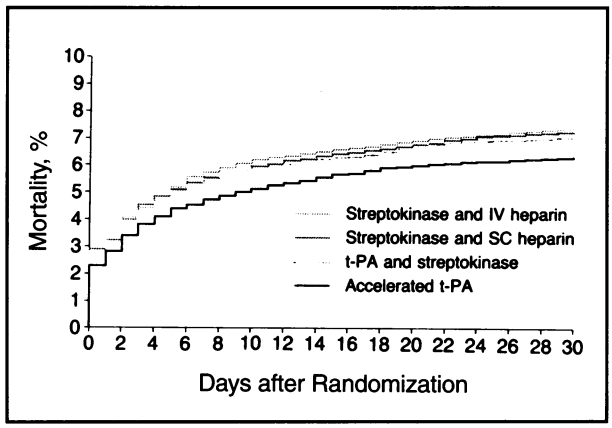

Figure 3.—The graph shows the 30-day mortality in the 4 treatment groups of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial. The group receiving accelerated tissue plasminogen activator (t-PA) had significantly lower mortality than any of the other treatment groups (from the GUSTO investigators[17]). IV = intravenous, SC = subcutaneous

and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)[17]—have compared the efficacy of streptokinase, anistreplase, and t-PA as well as different anticoagulation regimens in tens of thousands of patients. Neither GISSI-2 nor ISIS-3 revealed a significant difference in mortality between the various agents, but the use of streptokinase showed a significantly lower incidence of stroke in the ISIS-3 trial. The lack of demonstrable benefit of t-PA use over that of streptokinase in ISIS-3 and GISSI-2 was questioned because both studies used delayed subcutaneous rather than immmediate IV heparin after administering a thrombolytic drug. In addition, pilot data suggested that the efficacy of t-PA could be enhanced by administering the drug over a shorter period of time. These concerns provided impetus for the GUSTO trial, which randomly assigned 41,121 patients to one of four treatment groups: streptokinase with the immediate administration of IV heparin, streptokinase followed in four hours by subcutaneous heparin, accelerated t-PA—t-PA administered over 90 minutes with most of the dose given in the first 30 minutes, instead of the usual 3-hour infusion—followed by immediate IV heparin, or combined t-PA and streptokinase with IV heparin. Each group received aspirin and a β-blocker whenever possible. The accelerated t-PA regimen resulted in a 1% lower overall mortality than any of the other regimens, a difference that was significant (Figure 3). The mortality benefit came at the expense of a slight excess of hemorrhagic strokes with t-PA use compared with the streptokinase regimens. Nonetheless, the incidence of a combined end point of death or disabling stroke was lower with the accelerated t-PA regimen than with the streptokinase regimens. When subgroup analysis was done, the incremental benefit of t-PA use over that of streptokinase was greatest in patients younger than 75 years of age, with anterior MI, or presenting early after symptoms began (Figure 4). The explanation for the first subgroup effect is that the greater propensity for stroke in elderly patients with thrombolytic treatment was amplified by the use of t-PA. The explanation for the benefit of the use of t-PA over that of streptokinase in patients with anterior wall or early infarcts (or both) is most likely that these are the subsets most likely to benefit from thrombolysis in general, therefore affording greater statistical power to detect a difference between drugs.

Other considerations may enter into the decision to use t-PA. Because t-PA is less likely to decrease the blood pressure than streptokinase, the use of the former may be preferable in patients with borderline hypotension. Because streptokinase and anistreplase are antigenic, a blunted therapeutic response or allergic reaction may occur in patients who have previously received either drug. Such patients should also receive t-PA for coronary thrombolysis. Whereas t-PA is considerably more costly than streptokinase, the incremental cost per year of life saved (based on GUSTO results) compares favorably with other interventions employed in standard medical practice.[18]

In summary, the use of t-PA appears to afford a modest but statistically significant mortality benefit over that of streptokinase when given in an accelerated-dose regimen and followed by IV heparin. Patients older than 75 years, however, do not achieve this benefit because of an increased risk of stroke. Therefore, in most cases, eligible patients older than 75 years should be treated with streptokinase. In patients who receive streptokinase, there is no convincing evidence of a benefit from full-dose IV heparin over subcutaneous heparin. In patients with hypotension or recent exposure to streptokinase, it may be prudent to use t-PA, even in elderly patients.

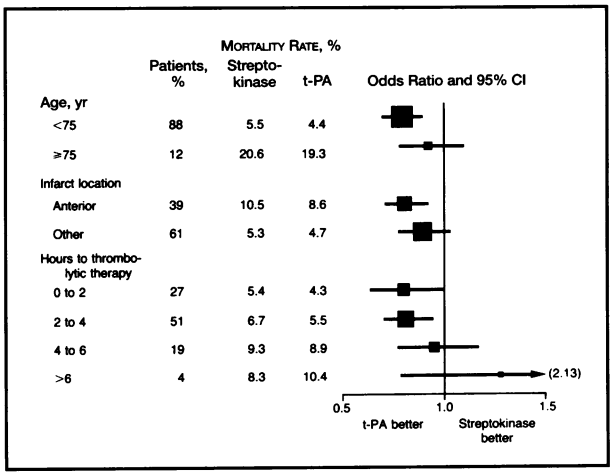

Figure 4.—Subgroup analysis is shown of mortality in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial. The subgroups showing the greatest incremental benefit of accelerated tissue plasminogen activator (t-PA) over streptokinase regimens were younger than 75 years, had an anterior wall infarct, and were patients in whom thrombolytic therapy was started earlier (from the GUSTO investigators[17]). CI = confidence interval

TABLE 3.—Indications for Coronary Angioplasty in Acute Myocardial Infarction

Coronary Angioplasty	Indication for Use
Primary	As an alternative to thrombolytic therapy
Primary	In patients with contraindications to thrombolytic therapy or in patients unlikely to benefit from thrombolysis—for example, those with cardiogenic shock
Rescue	In patients who have received thrombolytic therapy that is suspected or proved to have failed
Adjunctive	In patients initially treated with thrombolysis who subsequently show either spontaneous or easily inducible ischemia

Percutaneous Transluminal Coronary Angioplasty

As described earlier, the focus of current therapy for acute MI is reperfusion of the infarct-related artery. With increasing awareness of the limitations of thrombolytic agents—for example, contraindications to their use, complications related to bleeding, and failure to restore perfusion in as many as a third of cases—the role of percutaneous transluminal coronary angioplasty (PTCA) is becoming better defined. Table 3 lists four situations in which PTCA may be useful in patients with acute MI.

Initially, several small series of consecutive patients demonstrated the feasibility and efficacy of primary angioplasty for acute MI.[19] Subsequently, several randomized trials compared the use of primary PTCA with thrombolytic therapy.[20-22] In these trials, PTCA was accomplished in an average time of less than 60 minutes from hospital presentation. In the Primary Angioplasty in Myocardial Infarction (PAMI) trial,[20] 395 patients were randomly assigned to receive primary PTCA versus t-PA. The combined incidence of death and nonfatal reinfarction was lower in the group receiving PTCA. In addition, no strokes occurred in the PTCA group, versus seven cases in the t-PA group. In a randomized trial from the Netherlands comparing the use of streptokinase with that of primary PTCA, the principal end points of recurrent ischemia, ejection fraction, and coronary patency all favored the use of primary PTCA.[21] There were no significant differences in death or stroke rates, however. Results from a Mayo Clinic (Rochester, Minnesota) study revealed no significant difference between the use of primary PTCA or t-PA in left ventricular function or mortality,[22] but patients in the PTCA group had briefer hospital stays, fewer readmissions within six months, and lower six months' follow-up cost. Thus, in institutions offering prompt access to a cardiac catheterization laboratory with highly experienced operators, primary PTCA is a reasonable alternative and perhaps even a superior therapeutic strategy to thrombolysis. The greatest use of PTCA, however, is in a patient with a contraindication to thrombolysis who would otherwise be precluded from achieving reperfusion.

The concept of rescue angioplasty emerged with the increasing recognition that thrombolytic therapy achieved patency rates of only 60% to 80%. The Randomized Evaluation of Salvage Angioplasty With Combined Utilization of Endpoints (RESCUE) trial enrolled patients who had an occluded infarct-related artery demonstrated by coronary angiography despite treatment with a thrombolytic agent and who had an onset of chest pain within eight hours of enrollment.[23] Subjects were randomly selected to receive either conservative therapy (aspirin, heparin, and coronary vasodilators) or conservative therapy plus PTCA. In 92% of patients with occluded vessels, PTCA was successful, and the incidence of the combined end point of death or severe heart failure was substantially reduced in this group. The major obstacle to the strategy of rescue angioplasty, however, has been to identify patients in whom thrombolysis has failed without doing early coronary angiography in every case. This problem arises because the clinical markers of thrombolytic failure—persistent pain, persistent ST-segment elevation, the absence of reperfusion arrhythmias—have only modest predictive value. Thus, the successful application of rescue angioplasty in clinical practice may be impeded because clinicians hoping to achieve the beneficial outcome noted in the RESCUE trial would have to submit many patients to emergent coronary angiography to identify a subset with failed thrombolysis.

The role of deferred adjunctive PTCA following thrombolytic therapy was addressed by two large trials, phase II of the Thrombolysis in Myocardial Infarction study (TIMI II) and the Should We Intervene Following Thrombolysis? (SWIFT) trial.[24,25] In the TIMI II trial, an invasive strategy of angiography and PTCA attempted early (18 to 48 hours after thrombolysis) was compared with a conservative strategy in which angiography and PTCA were performed only if there was recurrent spontaneous ischemia or ischemia noted on predischarge exercise testing. Of the patients in the invasive arm, 57% underwent PTCA compared with 13% in the conservative arm. There was no significant difference between groups in the incidence of death, reinfarction, or left ventricular function at either six weeks or one year of follow-up. The results of the SWIFT trial were similar. Thus, angiography and PTCA need not be done on every patient after thrombolysis. The use of deferred PTCA should be reserved for patients with a complicated clinical course or those who continue to have spontaneous or easily induced ischemia.

The final indication for PTCA appears to be in treating patients with acute MI and cardiogenic shock. In the first GISSI trial, administering streptokinase appeared to be of no benefit over placebo in patients with acute MI and cardiogenic shock.[8] The mortality rates in both groups were dismal, at about 70%. Several investigators have reported survival to be markedly improved in patients with shock successfully treated with primary PTCA.[26] Thus, in patients presenting with acute MI and cardiogenic shock, the use of emergent PTCA should be pursued if logistically possible.

Coronary Artery Bypass Graft Surgery

There are no large, randomized clinical trials comparing the use of early coronary artery bypass grafting (CABG) with that of PTCA or thrombolytic therapy in the management of acute MI. Early CABG—within 24 hours of the onset of symptoms—can be done in selected patients with in-hospital mortality as low as 6%.[27] Similarly, nonemergent CABG can be performed in the days and weeks following acute MI without an increase in mortality.[28]

Because the strongest predictors of an adverse prognosis after acute MI are the extent of left ventricular dysfunction and recurrent ischemia (spontaneous or inducible), patients with one or both of these characteristics are most likely to benefit from early revascularization. When such patients are found to have left main or multivessel coronary artery disease or coronary lesions not readily amenable to PTCA, CABG may be the most appropriate revascularization strategy. Other possible indications for doing early CABG in patients with acute MI include failed thrombolysis, contraindications to thrombolysis, cardiogenic shock, or mechanical complications of acute MI such as acute ventricular septal defect or severe mitral regurgitation.

Adjunctive Pharmacologic Therapy

Nitrates

Several studies have investigated whether the routine use of nitrates reduces morbidity and mortality from acute MI. In a study before the development of thrombolytic therapy for acute MI, it was reported that administering IV nitroglycerin limited infarct size, reduced the incidence of cardiogenic shock and mural thrombus formation, and limited infarct expansion.[29] In addition, there was a significant reduction in mortality in treated patients. In a meta-analysis of trials of IV nitroglycerin therapy in acute MI conducted before the availability of thrombolytic therapy, there was a remarkable 35% to 40% reduction in mortality in treated patients.[30]

More recently, two large trials that investigated the effect of nitrates in conjunction with thrombolytic therapy have dampened the enthusiasm for the routine use of these agents. The GISSI-3 trial randomly assigned more than 19,000 patients either to receive IV nitroglycerin (on the first hospital day) followed by transdermal nitroglycerin or to an open control group.[31] Six-week mortality was not statistically different between the two groups. The Fourth International Study of Infarct Survival (ISIS-4[32]) randomly assigned 58,000 patients to receive controlled-release oral nitrate versus placebo. Again, there was no significant difference in mortality between the groups.

In conclusion, nitrates should be used whenever indicated to treat ongoing ischemia, ischemic pain, or pulmonary congestion. Recent data, however, do not support their routine use beyond these indications.

β-Blockers

The use of β-blockers in patients with acute MI was prompted by studies in animals that suggested that these agents might reduce infarct size, exert an antiarrhythmic effect, and prevent cardiac rupture. Acute β-blockade is clearly useful in subsets of patients with acute MI and ongoing ischemia or hyperdynamic circulation. Studies of the routine early administration of IV β-blockers in acute MI have been less convincing, however. In the Metoprolol in Acute Myocardial Infarction (MIAMI) trial,[33] the administration of IV metoprolol tartrate reduced early mortality by 13%, a result that was not statistically significant. In a study of 8,000 patients, the ISIS-1 showed a borderline-significant 15% reduction in one-week mortality using IV atenolol.[34] Both of these trials were conducted before the development of thrombolytic therapy. The use of early IV β-blockade in conjunction with thrombolytic therapy was investigated in the TIMI II trial.[24] Following thrombolysis with t-PA, patients were randomly assigned to receive either immediate IV metoprolol followed by oral metoprolol therapy or delayed oral metoprolol therapy beginning on day 6. The group receiving early IV metoprolol showed small reductions in the rates of reinfarction and recurrent ischemia during the initial six days of treatment; there was no significant difference in six-day mortality or in any end point at six weeks' follow-up. Thus, IV β-blockade during the acute phase may be marginally effective in reducing short-term recurrent ischemic events, and perhaps early mortality, after acute MI.

In contrast, the use of long-term oral β-blockade after myocardial infarction is a proven and powerful therapeutic intervention. Before the availability of thrombolytic therapy, several large randomized trials demonstrated 20% to 30% reductions in mortality with β-blockade at two to three years' follow-up (Figure 5).[3,35-37] Much of this benefit appears to be related to a reduced incidence of sudden death. Concern by some physicians about using β-blockers in patients with depressed left ventricular function has limited their application in this patient population. But closer examination of trials of β-blockade following acute MI reveals that patients with depressed left ventricular function actually have the greatest survival benefit from such therapy.[38,39]

There are unanswered questions regarding the long-term efficacy of β-blockade in patients who also receive thrombolysis, CABG, or PTCA. The efficacy of β-blockers when used with other classes of drugs such as angiotensin-converting-enzyme (ACE) inhibitors or antiarrhythmic agents is also uncertain. We think, however, that the striking mortality benefit documented in trials before thrombolytic therapy was available warrants the use of long-term β-blockade following myocardial infarction whenever possible.

Angiotensin-Converting-Enzyme Inhibitors

Recent work in both animals and humans has shown that infarct expansion and left ventricular remodeling

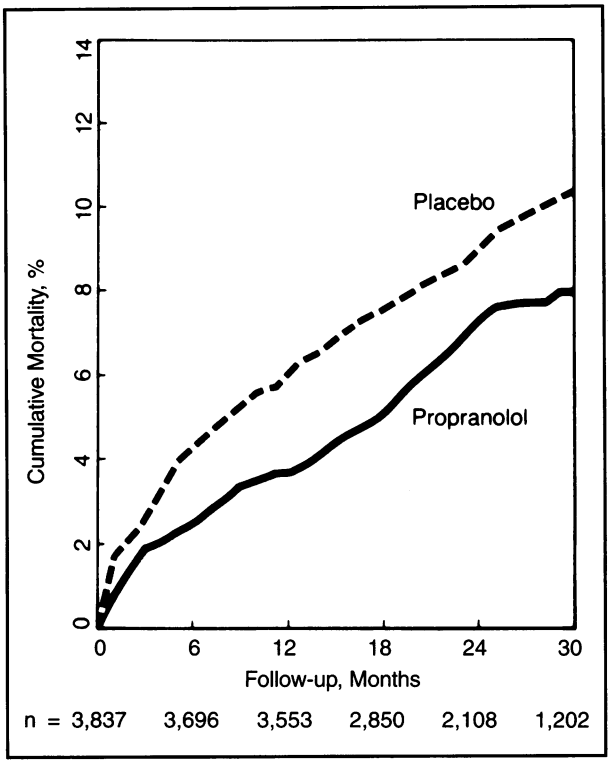

Figure 5.—Mortality data from the β-Blocker Heart Attack Trial (BHAT) shows that long-term propranolol therapy significantly reduced mortality after myocardial infarction (from the BHAT Research Group[35]). n = number of patients observed through each time point.

contribute to the late detrimental effects of acute MI and that administering ACE inhibitors can attenuate these processes.

The Survival and Ventricular Enlargement trial[40] randomly assigned 2,230 patients to receive either captopril or placebo starting 3 to 16 days after myocardial infarction. All patients had an ejection fraction of less than 40%, but none had symptomatic congestive heart failure. The administration of captopril reduced the rates of death, congestive heart failure, and recurrent acute MI by about 20% over a mean follow-up period of 42 months (Figure 6). Of note is that relatively high doses of captopril were used, with a target dose of 50 mg three times a day. Subgroup analysis indicated that the benefit from captopril use was independent of age, sex, or treatment with β-blocking or thrombolytic agents.

The Survival and Ventricular Enlargement trial raised the question of whether ACE inhibitors should be used after acute MI, regardless of the severity of left ventricular dysfunction. The GISSI-3 and ISIS-4 are large trials that investigated such generalized use of early oral ACE inhibitors. The GISSI-3 trial randomly assigned patients within 24 hours of acute MI and with a systolic blood pressure of more than 100 mm of mercury either to receive lisinopril or to an open control group.[31] At six weeks, active treatment resulted in an 11% decrease in mortality compared with the control group (0.8% absolute mortality difference). Of note, only 5% of these patients had an ejection fraction of 35% or less. The ISIS-4 trial, which randomly assigned patients to receive either placebo or captopril therapy within 24 hours of an acute MI, demonstrated a 9% reduction in mortality at four weeks.[32] Other studies have shown mortality benefits from the use of ramipril and zofenopril after acute MI.[41,42] Therefore, the salutary effect of ACE inhibitors is most likely a class effect and not limited to any individual compound.

Thus, ACE inhibitor treatment reduces mortality after acute MI, with the greatest benefit in patients with substantial left ventricular dysfunction. Because available data indicate a beneficial effect of ACE inhibitor therapy in patients treated concurrently with β-blockers,[40] our practice is to use both classes of drug whenever possible after acute MI.

Calcium Channel Antagonists

Although calcium channel blockers such as nifedipine, verapamil, and diltiazem provide a valuable therapeutic option in patients with ongoing angina, hypertension, or supraventricular tachycardia, studies investigating their routine use after acute MI have dimmed early expectations.

The trials assessing treatment with nifedipine in patients with acute MI have used several end points, including infarct size, reinfarction, and mortality.[43] The studies are problematic because several of them enrolled patients with unstable angina. Nifedipine appears to provide no benefit in terms of infarct size or rate of reinfarction. None of the trials has shown a reduction in either acute or long-term mortality. In fact, some trials

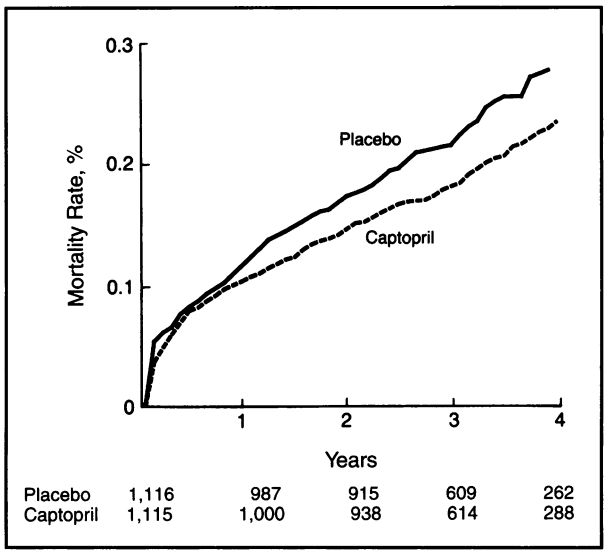

Figure 6.—Data from the Survival and Ventricular Enlargement trial shows a 19% risk reduction in long-term mortality with captopril therapy after myocardial infarction in patients with a left ventricular ejection fraction of less than 40% ($P = .02$). The number of patients observed at each time point is indicated at the bottom of the graph (from Pfeffer et al[40]).

have indicated a slight trend in the opposite direction. Thus, the use of nifedipine in myocardial infarction cannot be recommended.

The first Danish Verapamil Infarction Trial (DAVIT-I) randomly assigned 1,436 patients with acute MI to receive placebo or an IV bolus of verapamil followed by oral verapamil.[44] The study showed no significant difference in mortality or reinfarction at six months. The second Danish Verapamil Infarction Trial (DAVIT-II) randomly assigned more than 1,600 patients to receive placebo versus verapamil therapy, begun in the second week after acute MI.[45] At a mean follow-up of 16 months, there was no significant difference in mortality, but verapamil treatment significantly reduced the combined incidence of death or reinfarction. The effect appeared to be greatest in patients without heart failure.

Two trials have assessed the effects of diltiazem use in patients with acute MI. In the Diltiazem Reinfarction Study of non–Q-wave infarctions, treatment with diltiazem was initiated 24 to 72 hours after acute MI and continued for as long as 14 days.[46] Diltiazem use reduced the rate of early reinfarction by 51% and the frequency of severe angina by 49%. There was no significant effect on mortality, however. In the Multicenter Diltiazem Postinfarction Trial, 2,466 patients were randomly assigned to receive diltiazem or placebo within 3 to 15 days after acute MI.[47] Total mortality rates were nearly identical in the two treatment groups. A subgroup analysis revealed that in patients without radiographic pulmonary congestion, diltiazem use reduced the incidence of cardiac events (death or nonfatal infarction). In those patients with radiographic pulmonary congestion, diltiazem therapy was associated with an increase in the number of cardiac events. A similar effect was noted with respect to the ejection fraction, which was dichotomized at 40%.

Thus, the routine use of calcium channel antagonists cannot be justified in patients with acute MI on the basis of available data. The use of diltiazem or verapamil may be of benefit in patients with well-preserved left ventricular function, but these patients compose a group whose prognosis is good regardless of adjunctive drug therapy.

Magnesium Sulfate

The use of magnesium sulfate has several possible benefits in acute MI. In experimental models, it acts to dilate coronary vessels, stabilize cell membranes, decrease platelet aggregation, and reduce infarct size. Magnesium opposes calcium entry into cells, which has been implicated in reperfusion injury.[48] In addition, magnesium is inexpensive and safe to administer.

A meta-analysis of six trials of magnesium sulfate use in patients with acute MI revealed about a 50% reduction in mortality.[49] These data prompted the Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), which randomly assigned 2,300 patients to receive placebo versus IV magnesium sulfate, administered at a median of three hours after the onset of chest pain and continued for 24 hours.[50] The 28-day mortality was reduced by 24%, and the incidence of left ventricular failure was reduced by 25% in the magnesium-treated patients, results that achieved borderline significance. Subgroup analysis indicated that the benefit of magnesium use was independent of treatment with thrombolytic agents, aspirin, β-blockers, or calcium channel blockers. The promising results of LIMIT-2 prompted further investigation of the possible role of magnesium sulfate in the much larger ISIS-4 trial. In 58,000 patients,[32] administering IV magnesium sulfate did not appear to confer any mortality benefit compared with the open control group. The reason for the differences in the results of these two studies is unclear. The dose of magnesium was nearly identical. An intriguing hypothesis is that early administration of magnesium is required to achieve a therapeutic benefit. The median time to administration was three hours in LIMIT-2, but eight hours in the ISIS-4 trial. In animal models, the beneficial effects of magnesium therapy have been greatest when it is given before reperfusion, perhaps reducing reperfusion injury. Thus, it is possible that in ISIS-4, magnesium was administered too late to have a beneficial effect.

Thus, the therapeutic role of magnesium sulfate in acute MI remains in question. The drug can be administered safely to patients who do not have hypotension, renal failure, bradycardia, or heart block. Current data, however, make its use reasonable only in patients without contraindications in whom treatment can be initiated soon after the onset of symptoms.

Antiarrhythmic Agents

Prophylactic Lidocaine Hydrochloride

Lidocaine hydrochloride is effective in preventing primary ventricular tachycardia or fibrillation during the initial 24 to 48 hours after acute MI. In the past, the prophylactic use of lidocaine was recommended for patients with acute MI, regardless of the occurrence of "warning arrhythmias"—multifocal, frequent, or early premature ventricular contractions or nonsustained ventricular tachycardia. The results of a randomized trial and a meta-analysis of several smaller trials suggest that this strategy does not improve mortality and, in fact, may increase mortality during the treatment period.[51,52] Thus, the strategy of using prophylactic lidocaine in all patients with acute MI cannot be recommended.

Chronic Suppressive Antiarrhythmic Therapy

A substantial portion of the mortality following acute MI is the result of sudden cardiac death, presumably as a consequence of ventricular arrhythmias. Furthermore, frequent ventricular ectopy after acute MI has been identified as a risk factor for sudden death. Therefore, the attempted suppression of ventricular ectopy was a logical strategy to reduce mortality after acute MI. Unfortunately, the results of the Cardiac Arrhythmia Suppression Trial failed to support this concept.[53] In this trial, patients who had sustained an acute MI six days to two years before enrollment and had more than six

premature ventricular contractions per hour but no ventricular tachycardia episode longer than 15 consecutive beats were randomly assigned to receive either placebo or a type Ic antiarrhythmic agent (flecainide, encainide, or moricizine). An unexpected, significant increase in the incidence of sudden death and total mortality was found in the treated group. This adverse outcome was thought to be due to the drugs' proarrhythmic properties. Thus, the use of type Ic agents should be avoided in patients who have had acute MI, and any antiarrhythmic agent should be subjected to the careful scrutiny of large randomized, prospective trials before its use can be routinely recommended in these patients.

Amiodarone

Amiodarone is thought to have fewer proarrhythmic effects than conventional antiarrhythmic agents. Therefore, several trials have been undertaken to evaluate whether empiric amiodarone therapy can reduce mortality in patients who have had acute MI. Two small studies have been completed, and two larger trials are currently underway.

In a study in Poland, more than 600 patients who had had acute MI and who were ineligible to receive β-blockers (because of heart failure, diabetes mellitus, asthma, or peripheral vascular disease) were randomly assigned to receive either placebo or amiodarone (target dose, 400 mg per day) for a year.[54] Active treatment resulted in a borderline-significant reduction in cardiac mortality.

The Basel Antiarrhythmic Study of Infarct Size (BASIS) randomly assigned patients with complex ventricular arrhythmias after acute MI to one of three groups[55]: "individualized" antiarrhythmic therapy (quinidine, mexilitene, diisopyramide, flecainide, or sotalol, based on the results of Holter monitoring); low-dose empiric amiodarone, 200 mg per day; or open control. During the one-year follow-up, the mortality rates were 10% in the individualized therapy group, 5% in the amiodarone group, and 13% in the control group (Figure 7), representing a borderline-significant survival advantage for the amiodarone-treated patients.

These early small trials suggest that the use of amiodarone may improve survival in selected patients who have had acute MI. Several key questions remain unanswered, however. How does amiodarone therapy compare with the use of β-blockers in reducing mortality? Are there any additive benefits of the two classes of drugs? Which subgroups of patients derive the greatest benefit from amiodarone? Two larger trials in progress, the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) and the European Myocardial Infarction Amiodarone Trial (EMIAT), promise to shed light on these and other questions.

Aspirin and Oral Anticoagulants

Aspirin

The use of aspirin in acute MI was evaluated in the ISIS-2 trial.[9] In this study, 17,187 patients presenting

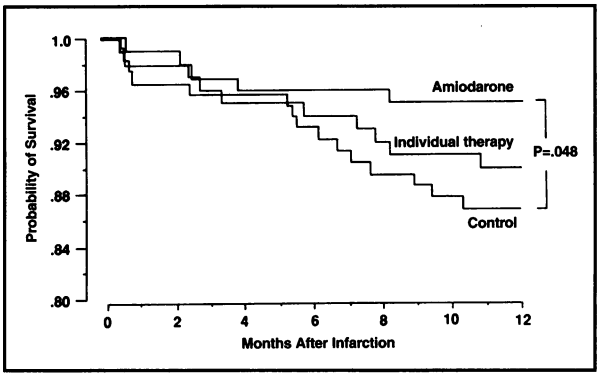

Figure 7.—Data from the Basel Antiarrhythmic Study of Infarct Size shows a borderline statistically significant ($P < .05$) improvement in survival with amiodarone therapy after myocardial infarction in patients with complex ventricular ectopy (from Burkart et al[55]).

within 24 hours of symptoms were randomly assigned to receive streptokinase, aspirin, both, or neither. Half of the initial aspirin dose was chewed for more rapid absorption. Mortality was reduced by 23% in the aspirin-only group, 25% in the streptokinase-only group, and 42% in the group receiving both aspirin and streptokinase. Thus, taking aspirin alone reduces the mortality from acute MI and appears to exert an additive effect when combined with streptokinase. Therefore, it is imperative that all patients receiving thrombolytic therapy be treated simultaneously with aspirin. In patients who are not candidates for thrombolysis, aspirin therapy should be initiated as soon as possible, whenever possible.

To date, six randomized, placebo-controlled trials of secondary prevention with aspirin have been conducted. Although the use of aspirin tended to reduce mortality, no significant benefit from therapy was shown in any single study, possibly because of inadequate statistical power. Pooling of data indicates that long-term aspirin therapy results in a 10% to 15% reduction in mortality and a 20% to 30% reduction in the incidence of reinfarction.[3,4] As a result, the use of aspirin is recommended for the secondary prevention of cardiovascular morbidity and mortality after acute MI.

Oral Anticoagulants

Warfarin sodium has been used to treat acute MI for more than 30 years. Until recently, however, there has been a dearth of well-controlled data supporting its use. The Warfarin Reinfarction Study (WARIS) was designed to assess the efficacy of warfarin use in reducing mortality and the incidence of reinfarction after acute MI.[56] Patients were randomly assigned at a mean of 27 days following acute MI to receive warfarin (target international normalized ratio [INR], 2.8 to 4.8) or placebo. An intention-to-treat analysis revealed a 24% reduction in mortality and a 34% reduction in the incidence of acute MI during a mean follow-up of 37 months (Figure 8). In addition, there was a 55% reduction in the incidence of stroke. This was achieved at the expense of a slightly higher incidence of major bleeding.

In the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial, patients were randomly assigned to receive an oral anticoagulant (INR 2.8 to 4.8) versus placebo.[57] More than 3,400 patients were randomly assigned within six weeks of discharge after acute MI and observed for a mean of 37 months. There was no significant difference in mortality or the incidence of recurrent acute MI or stroke as individual end points. Event-free survival—without death, acute MI, stroke, or bleeding—was significantly greater in the anticoagulant group, however.

Emboli from left ventricular mural thrombus due to acute MI account for 15,000 to 25,000 strokes each year. Mural thrombus formation is most likely to occur in patients with anterior MI with substantial regional wall motion abnormality, in whom the incidence may be as high as 30% to 40%.[58] The risk of suffering an event is greatest in the first ten days after the infarction, but persists for one to three months. A meta-analysis of anticoagulation trials suggests that the incidence of mural thrombus occurring after acute anterior MI can be reduced with these agents.[59] In addition, treatment with anticoagulants appears to reduce the rate of systemic embolization in patients with a known mural thrombus.

Although the administration of warfarin may reduce morbidity and mortality after acute MI, it is unclear whether its use confers greater benefit than that of aspirin or whether less intensive anticoagulation regimens would be equally effective with fewer bleeding complications. Patients at high risk for mural thrombus or with known mural thrombus should certainly be treated with systemic anticoagulation, initially with heparin and then with an oral anticoagulant.

Summary

In large part because of the interventions described in the preceding pages, the survival following hospital admission for acute MI has increased dramatically over the past 25 years. Survival over the first 30 days after hospital admission has risen from about 75% in 1970 to about 90% today.[60] Many therapeutic decisions faced by physicians, however, are not yet firmly grounded in the results of large, randomized, prospective clinical trials. There is still no substitute for sound and seasoned clinical judgment based on the assessment of each patient's condition.

Furthermore, the interactive effects among several interventions that are effective individually remain uncertain in many cases. Clearly, early thrombolytic therapy is a pivotal intervention to reduce mortality in acute MI. Percutaneous transluminal coronary angioplasty, if it can be performed expeditiously, may be an effective alternative to thrombolysis. The immediate use of aspirin and the early initiation of ACE inhibition have been shown to convey survival benefit with or without thrombolytic therapy. Long-term treatment with either aspirin or warfarin is indicated in suitable patients, but the optimal choice between these two drugs is not established. Immediate IV

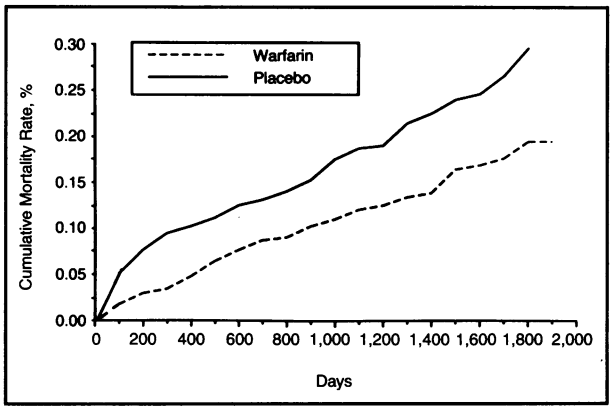

Figure 8.—A reduction in mortality after myocardial infarction is shown with warfarin therapy. The data are from the Warfarin Reinfarction Study. Much of the mortality reduction may be due to a reduced incidence of stroke (from Smith et al[56]).

β-blockade and the early use of nitrate preparations should be reserved for patients whose hemodynamic state or symptoms suggest a specific benefit; the ubiquitous application of these treatments has not been shown to reduce mortality, however. Because of the pronounced benefit of long-term oral β-blockade in reducing mortality after MI in trials done before the availability of thrombolytic therapy, it is reasonable to continue to use these agents. The benefit of long-term β-blockade is likely to be greatest in patients with reduced left ventricular function. We recommend the use of both a β-blocker and an ACE inhibitor, if tolerated. Antiarrhythmic drug therapy should be undertaken cautiously in patients who have had an MI and reserved primarily for patients with sustained, symptomatic, or hemodynamically compromising dysrhythmias. It is hoped that the role of amiodarone in these patients will be clarified by large, ongoing clinical trials.

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